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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,809	04/26/2002	Ronit Eisenberg	026549-000100US	1519

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EXAMINER

CROWDER, CHUN

ART UNIT	PAPER NUMBER
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1644

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/009,809

Applicant(s)

EISENBERG ET AL.

Examiner

Chun Crowder

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11/22/2006 and 1/29/2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 63-70 and 72-80 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 63-70 and 72-80 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 08/09/2006.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's telephone inquiry made 01/29/2007 regarding the Final Rejection, mailed 12/12/2006, is acknowledged. Upon further consideration, the previous Office Action, mailed 12/12/2006, is hereby vacated in view of the following Office Action.
2. This Office Action will be in response to applicant's arguments, filed 11/22/2006.
3. Applicant's IDS, filed 08/09/2006, is acknowledged and has been considered except for References 2, 3 and 4 for which have been considered only to the extent of the abstracts provided by applicant.
4. The three references attached in applicant's amendment as Exhibits have been listed on PTO-892.
5. Applicant is advised that should claims 79 and 80 be found allowable, claims 79 and 80 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 79 and 80 are objected to under 37 CFR 1.75 as being exact duplicates of claims 77 and 78, respectively.

Applicant is required to cancel the duplicate claims 79 and 80.
6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 63-70 and 72-80 are rejected under **35 U.S.C. 103(a)** as being unpatentable over Holgate et al. (British Medical Bulletin. 1992. 48;1:40-50) in view of Adridor et al. (Science 1993. 262:1569-1572) and Lin et al. (US Patent 5,807,746) for the same reasons set forth in the Office Action mailed 08/02/2006.

Applicant's arguments, filed 11/22/2006, in conjunction with the Exhibits 1-3 have been fully considered but have not been found persuasive.

Applicant argues that there is no reasonable expectation that once a cargo peptide is transported into a cell by a cell-penetrating peptide (CPP) the cargo peptide will retain its biological properties.

Applicant states that page 10 of the instant specification as well as the Table on page 9 of the Remark have shown four different cell-penetrating peptides (CPP) including the following:

human integrin $\beta 3$ (Hu Int) and Kaposi fibroblast growth factor (KFGF) (see Exhibit 2. Hawiger, 1997 Current Opinion in Immunology 9: 189-194, see page 189 in particular),

a Drosophila transcription factor (Dros) (Exhibit 3. Derossi et *al.* 1996 JBC 27 1(30): 18188- 18193, see page 18188 in particular), and

tanspotan 10 (TP-10) (Jones et al. Biochimica et Biophysica Acta 2005. 1745:207-214, see page 207 in particular. Reference on PTO-1449).

Applicant argues that when the above mentioned CPPs combined with two mast cell activation inhibitor domains cargo peptide G α i3 and G α t, only KFGF-G α i3 (SEQ ID NO:7) and KFGF- G α t (SEQ ID NO:12) have retained inhibitory effects on mast cell degranulation.

Therefore, applicant concludes that even though there is a reasonable expectation that any cell-penetrating peptide (CPP) would transport any cargo peptide across a cell; it is still unpredictable whether the cargo peptide would retain its biological function in the cell.

This is not found persuasive for the following reasons:

The Examiner acknowledges that the two peptides KFGF-G α i3 (SEQ ID NO:7) and KFGF- G α t (SEQ ID NO:12) that have retained their inhibitory effects on mast cell degranulation have the same CPP that is recited in the instant claims (KFGF peptide with amino acid sequence of AAVALLPAVLLALLAP recited in SEQ ID NO:3) (see claim 63 and page 4 of the instant specification); as such, it is clear that CPP with amino acid sequence of the instant claimed SEQ ID NO:3 is able to transport different cargo peptides (e.g. G α i3 and G α t) and retain their activity.

Further, Lin et al. specifically demonstrate using multiple working examples that the KFGF peptide AAVALLPAVLLALLAP (instant claimed SEQ ID NO:3) is capable of not only importing signal sequence-containing peptides but also maintaining the functions of the transported cargo peptides such as the nuclear localization sequence of acidic FGF (see columns 14-15 in particular) and functional domain of the nuclear factor kB (see columns 16-17 in particular).

Art Unit: 1644

Therefore, the claimed CPP peptide AAVALLPAVLLALLAP (instant SEQ ID NO:3) has been shown to be able to transport four different cargo peptides including G α i3 and G α t (both disclosed in the instant specification), nuclear localization sequence of acidic FGF (see columns 14-15 in Lin et al) and functional domain of the nuclear factor kB (see columns 16-17 of Lin et al) and maintain their biological activities.

Given that the claimed CPP peptide AAVALLPAVLLALLAP (instant SEQ ID NO:3) and the mast cell inhibitory cargo peptide KNNLKECGLY (instant SEQ ID NO:1) have the identical sequences as the prior art peptides taught by Lin et al. and Adridor et al, respectively, and these two peptides are linked via the same linker as taught by the Lin et al, it is predictable and expected that AAVALLPAVLLALLAP (instant SEQ ID NO:3) would be able to transport peptides such as KNNLKECGLY (instant SEQ ID NO:1) and retain their biological activities including inhibitory effect on mast cell degranulation.

Regarding applicant's assertion that Jones et al. (Biochimica et Biophysica Acta 2005. 1745:207-214) teach the field of CPP is unpredictable (see page 8 of the Remarks), it is noted the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. In this case, Jones et al. teach that the effect of cell-penetrating peptides can be unpredictable due to limited knowledge of the mechanisms associated with mast cell exocytosis as such it is unpredictable if CPP peptides can be used for "preventing mast cell degranulation in a subject" (see Office Action mailed 08/02/2006). In fact, Jones et al. teach that the delivery of peptide cargoes using CPP is a valid method for studying and modulating signal transduction pathways (e.g. see page 207, in particular).

Furthermore, applicant states that there is no additional available evidence of the unpredictability of bioactivity of peptides transported by cell-penetrating peptide (see page 7 of the Remark filed 11/22/2006).

Therefore, applicant's arguments that the filed of CPP is unpredictable have not been found persuasive.

Applicant further argues that there is no reasonable expectation that once a cargo peptide is transported into a cell by a cell-penetrating peptide (CPP) the peptide will retain its biological properties. However, applicant fails to provide any objective evidence of record that show the claimed SEQ ID NO:1 when transported into a cell by a CPP of SEQ ID NO:3 will not retain the biological properties of the SEQ ID NO:3.

Moreover, applicant argues that even though there is a reasonable expectation that any cell-penetrating peptide (CPP) would transport any cargo across a cell; it is still unpredictable whether the cargo would retain its biological function in the cell.

In addition, applicant asserts that Aridor et al. only teach that anti-allergy peptides have biological activity but not cell-penetrating peptide (CPP), while the instant claims are drawn to a combination of a cell-penetrating peptide (CPP) (SEQ ID NO:3) and an anti-allergy peptide (SEQ ID NO:1).

In response to applicant's arguments that there is no expectation of success of combining the teachings of the reference, the examiner recognizes that obviousness requires only a reasonable expectation of success; the prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success See MPEP 2143.02.

It is further noted that in considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom In re Preda, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968). See MPEP 2144.01.

Furthermore, specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA). In re Burckel is cited in MPEP 716.02.

In this case, the teachings of Aridor et al. pertaining to the biological effect of the peptide KNNLKECGLY in inhibiting mast cell degranulation for targeting intracellular targets and the teachings of Lin et al. indicating success in importing biologically active molecules in to cell by linking cell-penetrating peptides (e.g. AAVALLPAVLLALLAP) to the biological molecules via linkers would have led one of ordinary skill in the art at the time the invention was made to combine the references to arrive at the claimed invention of method of inhibiting mast cell degranulation using a complex molecule comprising cell-penetrating peptide AAVALLPAVLLALLAP linked via a linker to the biological active peptide KNNLKECGLY capable of inhibiting mast cell degranulation.

In response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combination of references. See MPEP 2145.

Here, given the teachings of Holgate et al regarding the role of mast cell degranulation in asthma, and the teachings of Aridor et al. and Lin et al. providing the method of inhibiting mast cell degranulation by synthetic peptide KNNLKECGLY and methods of delivering biological molecule into cell using of importation competent signal peptide AAVALLPAVLLALLAP, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success in producing the claimed methods.

In conclusion, applicant's arguments in conjunction with the Exhibits 1-3 and Table on page 9 of the Remark fail to demonstrate that the claimed AAVALLPAVLLALLAP (instant SEQ ID NO:3) is unpredictable for retaining biological activities of the peptides it transport.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. Claims 64 and 65 are rejected under **35 U.S.C. 103(a)** as being unpatentable over Holgate et al. (British Medical Bulletin. 1992. 48;1:40-50) in view of Adridor et al. (Science 1993. 262:1569-1572) and Lin et al. (US Patent 5,807,746) as applied to claim 63 above, further in view of Avruch et al. (US Patent 6,103,692) and Jackson et al. (J. Am. Chem. Soc. 1994. 116:3220-3230) for the same reasons set forth in the Office Action mailed 08/02/2006.

Applicant's arguments and the examiner's rebuttal are essentially the same as above in Section 7.

9. Claims 63-70 and 72-80 are provisionally rejected on the ground of **nonstatutory obviousness-type double patenting** as being unpatentable over claims 1-44 of copending USSN 10/465,826, and claims 1-15 of the copending USSN 11/214,588 for the same reasons set forth in the Office Action mailed 08/02/2006.

Applicant argues that the rejection on the ground of provisional double patenting must be withdrawn when it is the sole remaining basis for rejection.

Given that the rejections under 35 U.S.C. 103(a) have been maintained for reasons stated above in Sections 7 and 8 and a terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) has not been filed; the rejection on the basis of double patenting will be maintained until such a time that allowable subject matter is determined or a terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) is timely filed.

10. Upon further consideration as well as applicant's amendment, the previous rejection under **35 U.S.C. 112, first paragraph** set forth in the previous Office Action, mailed 08/02/2006 has been withdrawn.

11. *Conclusion: no claim is allowed.*

Art Unit: 1644

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Crowder whose telephone number is (571) 272-8142. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chun Crowder, Ph.D.

Patent Examiner

February 8, 2007

Phillip Gambel
PHILLIP GAMBEL, PH.D. JD
PRIMARY EXAMINER
TC 600
2/8/07